vector, said vector comprising

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said vector, wherein said transcriptional regulatory sequence functions in said cell so that replication of the vector occurs in said cell, wherein said coding region is selected from the group consisting of E1 a E1b, and E2 and E4 coding regions.

79. (new) A method of producing a tissue-specific replication-conditional adenovirus vector, said vector comprising a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said vector, comprising culturing the isolated cell of claim 78 and recovering said vector from said cell.

80. (new) An isolated cell containing a tissue-specific replication-conditional adenovirus virion, said virion comprising

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said virion, wherein said transcriptional regulatory sequence functions in said cell so that replication of the virion occurs in said cell wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions.

REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 1, 3-8 and 55-80, the currently pending claims. Claim 2 has been canceled, without prejudice to refiling. Claims 1, 3-8, 56, 57, 59, 60, 61, 68 and 74 have been amended. No new matter is added.

Claims 77-80 are new. Support for the language of the new claims is as follows. The term "tissue-specific" finds support on page 14, line 26 of the present application. The term "replication-conditional" finds support in the summary of the invention, page 6. line 16. While the word "conditional" is not used in the present specification, the common definition of the term is an adjective modifying a subject, for example viral replication, which is determined or to be determined by something else (American Heritage Dictionary). It is clear from the discussion of preferential replication of adenovirus on page 10, lines 3-14 of the specification, that replication of the adenoviral vector in the present invention is dependent on tissue specific factors, and therefore is

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Cancel claim 2.

1. (amended) [An] A cytolytic replication competent adenovirus vector comprising an adenovirus gene essential for replication under transcriptional control of a cell type-specific transcriptional response element (TRE).

3. (amended) [An] The adenovirus vector according to claim [2] 1, wherein the gene essential for replication is an adenoviral early gene.

4. (amended) [An] The adenovirus vector according to claim 3, wherein the adenovirus early gene is E1A.

5. (amended) [An] The adenovirus vector according to claim 3, wherein the adenovirus early gene is E1B.

6. (amended) The adenovirus vector of claim [2] 1, wherein the gene essential for adenoviral replication is the adenovirus E4 gene.

7. (amended) The adenovirus vector of claim [2] 1, wherein the gene essential for adenoviral replication is an adenovirus late gene.

8. (amended) [An] The adenovirus vector of claim 1, wherein the cell type-specific TRE is prostate cell specific.

56. (amended) The adenovirus vector of claim [2] 1, wherein the TRE is selected from the group consisting of a promoter and an enhancer.

57. (amended) The adenovirus vector of Claim [2] 1, wherein the cell-type specific TRE is selected from the group consisting of an alpha fetoprotein TRE, a DF3-TRE, a tyrosinase-TRE, a CEA-TRE, a surfactant protein-TRE, and an ErbB2-TRE.

59. (amended) The vector of claim [2] 1, wherein said vector contains a heterologous coding sequence that is expressed from said vector.

60. (amended) The vector of claim [2] 1, wherein said vector is encapsulated in an adenovirus coat.

61. (amended) [An] A cell comprising a replication competent adenovirus vector comprising an adenovirus gene essential for adenoviral replication under transcriptional control of a cell type-specific transcriptional response element (TRE), wherein said adenovirus gene essential for adenoviral replication is selected from the group consisting of E1A, E1B, E2 and E4, and wherein said TRE functions in said cell so that replication of the vector occurs in said cell.

68. (amended) [An] A cell comprising a cell-type specific replication competent adenovirus vector encapsulated in an adenovirus coat, said vector comprising an adenovirus gene essential for adenoviral replication under transcriptional control of a cell type-specific transcriptional response element (TRE), wherein said adenovirus gene essential for adenoviral replication is selected from the group consisting of E1A, E1B, E2 and E4, and wherein said TRE functions in said cell so that replication of the encapsulated vector occurs in said cell.

74. (amended) A method of producing a cell-type specific replication competent adenovirus vector encapsulated in an adenovirus coat, said vector comprising an adenovirus gene essential for adenoviral replication under transcriptional control of a cell type-specific transcriptional response element (TRE) comprising

culturing a cell comprising a cell-type specific replication competent adenovirus vector encapsulated in an adenovirus coat, said vector comprising an adenovirus gene essential for adenoviral replication under transcriptional control of a cell type-specific transcriptional response element (TRE) wherein said adenovirus gene essential for adenoviral replication is selected from the group consisting of E1A, E1B, E2 and E4, and wherein said TRE functions in said cell so that replication of the encapsulated vector occurs in said cell; and

(b) recovering said encapsulated adenoviral vector from the culture.

Add the following new claims:

77. (new) A tissue-specific replication-conditional adenovirus vector comprising:

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for the replication of said vector, wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions.

78. (new) An isolated cell containing a tissue-specific replication-conditional adenovirus vector, said vector comprising

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said vector, wherein said transcriptional regulatory sequence functions in said cell so that replication of the vector occurs in said cell, wherein said coding region is selected from the group consisting of E1 a E1b, and E2 and E4 coding regions.

79. (new) A method of producing a tissue-specific replication-conditional adenovirus vector, said vector comprising a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said vector, comprising culturing the isolated cell of claim 78 and recovering said vector from said cell.

80. (new) An isolated cell containing a tissue-specific replication-conditional adenovirus virion, said virion comprising

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said virion, wherein said transcriptional regulatory sequence functions in said cell so that replication of the virion occurs in said cell wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions.

encompassed by the term "conditional".

Support for the term "heterologous" may be found on page 19, line 2; "transcriptional regulatory sequence" on page 9, line 15; "operably linked" on page 12, line 10; "coding region of a gene" on page 19, line 8; "essential for replication" on page 20, line 18, "E1a, E1b and E2 and E4 coding regions" on page 24, line 10; and "virion" on page 24, line 29. Entry of the claims is requested.

A supplemental IDS is attached herewith, which recites the title of non-patent publications, as requested by the Examiner. Consideration of the references is requested.

Applicants have amended the claims to overcome the objections cited by the examiner. Withdrawal of the objections is requested.

Claims 1-8, 59, 61 and 67 have been provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-8, 28-31, 33-34, 42 and 44-45 of co-pending Application no. 09/151,376. Applicants respectfully submit that when a provisional rejection of this type is made, it is proper to issue one of the applications and allow a terminal disclaimer to be filed in the other, and agree to provide a suitable terminal disclaimer at such time as a patent is issued.

Claims 1-6, 8, 59, 61 and 67 have been rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1, 3-6, 8-9, and 12 of U.S. Patent no. 5,698,443. Claims 1-5, 7-8, 59, 61-62, 64-69 and 71-76 have been rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-5, 12-14, 21-23 and 27-32 of U.S. Patent no. 5,871,726. Claims 1-5, 7, 59, 61, 64, 67-68 and 71-76 have been rejected under the judicially created doctrine of obviousness type double patent over claims 1-6, 14-16, 18, 20, 23-27, 30, 32 and 37-38 of U.S. Patent no. 6,197,293. Claims 1-5, 56-59, 61-66 and 68-73 have been rejected under the judicially created doctrine of obviousness type double patent over claims 1, 3-6, 11 and 37 of U.S. Patent no. 6,254,862.

Applicants agree to provide a terminal disclaimer for the present claims over U.S. Patent no. 5,698,443, U.S. Patent no. 5,871,726, U.S. Patent no. 6,197,293, and U.S. Patent no. 6,254,862, as appropriate, upon indication of allowable subject matter.

Claims 2-5 and 8 have been rejected under 35 U.S.C. 112, second paragraph. Claim 2 has

been cancelled and claims 3-5 and 8 have been amended in accordance with the Examiner's suggestion. Withdrawal of the rejection is requested.

Claims 1-8 and 55-76 have been rejected under 35 U.S.C. 112, first paragraph. Without conceding to the correctness of the rejection, independent Claims 1, 61, 68 and 74 have been amended to recite a replication competent adenovirus vector. Withdrawal of the rejection is requested.

Claims 1-6, 8 and 55-76 have been rejected under 35 U.S.C. 102 (e) as anticipated by Gregory *et al.*, US2001/0053768. The Office Action states that Gregory *et al.* teaches a method of treating mammalian cancer cells by administering a replication competent adenoviral vector comprising a therapeutic gene and a disease specific gene regulatory region. Applicants respectfully submit that the present claims are not anticipated by Gregory *et al.*

As stated in the summary of the invention, Gregory *et al.* provides a method for "amplifying the effect of the therapeutic gene carried by the replication competent adenoviral vector". The application is therefore directed at methods of increasing the expression of a therapeutic gene in the targeted tissue. As defined by Gregory *et al.*, therapeutic genes are foreign genes expressed from the replication competent adenoviral vectors, and specifically are not present in wild-type adenovirus (paragraph 17).

In contrast, Applicants invention is directed at replication competent adenovirus which utilize cell type-specific transcriptional regulatory elements operably linked to native adenoviral genes. The constructs are designed such that the cell type-specific transcriptional regulatory element facilitates replication of the adenovirus and corresponding death of particular host cells and not others , (as described in the specification, e.g., on page 40, lines 7-9 and on page 44, lines 7-8). In contrast to the teachings of Gregory *et al.*, the present invention relies on selective cytolysis of target cells. As such, the present claims are distinguished from Gregory *et al.* Withdrawal of the rejection is requested.

Claims 1-3, 5-6 and 55 have been rejected under 35 U.S.C. 102(b) as anticipated by Friedman *et al.* (Transcriptional Control Mechanism, pp 421-435, 1987). The Office Action states that Friedman *et al.* replaced the normal regulatory element, E1A, with a tissue specific promoter. Applicants respectfully submit that the presently claimed invention is not anticipated by Friedman *et al.*

The present claims are directed to a replication competent adenovirus vector. One of the

genes essential for virus replication is E1A. By replacing the E1A gene with the albumin promoter, Friedman *et al.* necessarily created a vector that is *not* replication competent. Therefore, the reference fails to meet all the limitations of the claims. Withdrawal of the rejection is requested.

Claims 1-6, 8 and 55-76 have been rejected under 35 U.S.C. 103 as unpatentable over Gregory *et al.*, taken with Bohinski *et al.*, Abe *et al.*, Grooteclaes *et al.* The Office Action states that Abe, Grooteclaes and Bohinski teach tissue specific promoters.

Applicants respectfully submit that the cited combination of references does not make obvious the claimed invention. As discussed above, Gregory *et al.* fails to teach a cytolytic replication competent adenovirus, and is directed to adenovirus as a vector to deliver therapeutic foreign genes to a targeted cell. The secondary references fail to remedy the deficiencies of Gregory *et al.* The secondary teachings disclose specific transcriptional response elements, but provide no teaching or motivation for using such elements to construct an adenovirus vector in which the adenovirus causes selective cytolysis of target cells.

In viewing the combination of cited art, a person of ordinary skill in the art would lack the guidelines necessary to practice the claimed invention. The essential feature of providing a cytolytic replication competent adenovirus is not provided in the art, and requires an inventive step well beyond routine experimentation. In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 1-7, 55-56 and 60 have been rejected under 35 U.S.C. 103(a) as unpatentable over McCormick, U.S. patent no. 5,667,178, taken with Glazenburg *et al.*, Berkener *et al.*, Roth *et al.* McCormick infects neoplastic and non-neoplastic cells with a wild-type adenovirus and shows that wild type virus kills both types of cells. Glazenburg teaches a microorganism under control of a nucleotide specific for the cell. Roth teaches a method for killing tumor cells using a recombinant adenovirus encoding a tumor suppressor gene. Berkner teaches advantages of adenovirus.

Applicants respectfully submit that the cited combination of references does not make obvious the claimed invention. McCormick *et al.* states that the adenoviral E1B gene product forms a complex with p53, an antiviral host cell protein, thereby inactivating the host p53 protein. In the invention of McCormick *et al.*, a recombinant adenovirus is provided which comprises an E1b locus that does not bind to p53. It is stated that neoplastic cells which lack functional p53 are able to support replication of such a recombinant adenovirus, while non-neoplastic cells which have functional p53 do not. McCormick *et al.* fails to teach a replication competent adenovirus comprising an adenovirus gene essential for replication under the control of a tissue specific TRE.

McCormick *et al.* is combined with Glazenburg *et al.* Glazenburg *et al.* teaches very generally the idea that a virus might be mutated so that the desired effect, immunogenicity, is achieved, without the undesired effect, cytocidal activity. Even with respect to tumors, Glazenburg does not suggest a cytotoxic virus, but rather one that promotes an immune response against the tumor cell. In this way, Glazenburg *et al.* teaches away from the present invention, as the desired effect of the presently claimed invention is to increase targeted cytotoxicity, while the desired effect of Glazenburg *et al.* is to decrease cytotoxicity.

Further, Glazenburg *et al.* fails to provide any specific teaching that would permit one of skill in the art to construct an adenovirus vector according to the present invention. The suggestions of Glazenburg *et al.* are so vague that, rather than the guidelines necessary for reasonable expectation of success, one is provided with nothing more than a vast research agenda, requiring substantial experimentation and invention.

The combination of McCormick *et al.* and Glazenburg *et al.* fail to provide reasonable guidelines and teaching for a cytolytic replication competent adenovirus vector. The teachings of Roth *et al.* fail to remedy the defects of the first two references. Roth *et al.* is directed to the use of adenovirus as a vector for a therapeutic gene, and does not consider the possibility of utilizing the cytotoxicity of the adenovirus itself as a therapeutic moiety. In fact, the preferred vector for Roth *et al.* is "replication defective viruses in which a viral gene essential for replication and/or packaging has been deleted from the adenoviral vector construct, allowing the p53 expression region to be introduced in its place." One of skill in the art would not be motivated by Roth *et al.* in combination with McCormick *et al.*, and Glazenburg et al., to produce a cytotoxic replication competent adenovirus.

Berkner is a review of techniques for the expression of heterologous genes in adenovirus, and does not teach or suggest methods of modifying adenovirus to be therapeutic in the absence of heterologous genes products.

In view of the above remarks, Applicants respectfully submit that the cited combination of art does not teach or suggest the presently claimed invention. Withdrawal of the rejection is requested.

Claims 1-8 and 55-76 have been rejected under 35 U.S.C. 103(a) as unpatentable over McCormick, taken with Glazenburg *et al.*, Berkener *et al.*, and Roth *et al.*, and further in view of Bohinski *et al.*, Abe *et al.*, Grooteclaes *et al.*, Richards *et al.*, Vile *et al.*, Riegman *et al.*, and Watanabe *et al.* The rejection is as applied above, and adding the teachings of tissue specific promoters.

Applicants respectfully submit that the cited combination of references does not make

obvious the claimed invention, as discussed above. While the teachings of Abe *et al.*, Grooteclaes *et al.*, Richards *et al.*, Vile *et al.*, Riegman *et al.*, and Watanabe *et al.* provide for certain specific transcriptional response elements, there is no teaching or motivation for using such elements to construct a replication competent adenovirus vector in which the adenovirus causes cytolysis of target tissue through expression of native adenoviral genes.

In viewing the combination of cited art, a person of ordinary skill in the art would lack the guidelines necessary to practice the claimed invention. The essential feature of providing a cytolytic replication competent adenovirus is not provided in the art, and requires an inventive step well beyond routine experimentation. In view of the above amendments and remarks, withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-004CON.

Respectfully submitted,

Date: May 29, 2002

By: _____
Pamela J. Sherwood, Ph.D.
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231